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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,561	08/25/2003	Michael David Bentley	034848/268660	3230

21968 7590 08/08/2006

NEKTAR THERAPEUTICS  
150 INDUSTRIAL ROAD  
SAN CARLOS, CA 94070

EXAMINER
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HEARD, THOMAS SWEENEY

ART UNIT	PAPER NUMBER
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1654

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/647,561	<b>Applicant(s)</b> BENTLEY ET AL.	
	<b>Examiner</b> Thomas S. Heard	<b>Art Unit</b> 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 May 2006.  
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3, 5-19, 21, 23, 24, 26 and 27 is/are pending in the application.  
4a) Of the above claim(s) 24 is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 1-3, 5-19, 21, 23, 26 and 27 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.  
10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>8/25/2003</u> .   | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election without traverse of the species biphalin in the reply filed on 5/24/2006 is acknowledged. Applicants elected species is readable on claims 1-3, 5-19, 21, 23, 26, and 27. The Applicants have canceled claims 4, 20, 22, and 25. Claim 24 is withdrawn from consideration as not being readable on the elected species.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not understood what is being claimed by apparent "absence of non-covalent bonds." Absent of covalent bonds for the PEG to biphalin? Clarification is required.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 5-19, 21, 23, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delgado C, Francis GE, Fisher D., "The uses and properties of PEG-linked proteins," Crit Rev Ther Drug Carrier Syst. 1992;9(3-4):249-304 and Wu D, Pardridge WM., "Neuroprotection with noninvasive neurotrophin delivery to the brain," Proc Natl Acad Sci U S A. 1999 Jan 5;96(1):254-9.

Delgado et al teaches the beneficial uses and properties of PEG-linked proteins and peptides. Delgado et al teaches the generic benefits of PEGylating a protein which are increased plasma half-life, reduced renal clearance, reduced cellular clearance, reduced proteolysis, reduced immunoclearance, reduced immunogenicity and antigenicity, and increased solubility, among other properties of the PEG-protein conjugates. Unrelated PEG-proteins are shown to have these beneficial properties demonstrating the broad acceptance of the conjugated PEG to the proteins. Delgado et al further teaches mono-pegylation, bi- and multiple-pegylation, N-terminal PEGylation and PEGylation in ranges from 700 to 70,000 MW readable upon n ranging from 10 to 2000 for  $-\text{CH}_2\text{CH}_2\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-$  in claim 27. See entire Review Article. Delgado et al does not teach the pegylation of the neuropeptide biphalin.

Wu et al teaches a neuropeptide (BDNF) that has been PEGylated (2000 MW) and further chemically modified to include a biotin/OX26Mab composition (diagnostic agent by the Applicant's specification) on the terminus of the PEG for transport across the blood brain barrier (BBB). Thus, the neuropeptide (BDNF) had the benefits of PEGylation taught by Delgado et al with the added capacity to transport across the BBB. Wu et al states that "there are more than 30 known neurotropic factors and there

molecules may prove to be powerful neuropharmaceuticals should they be enabled to undergo transport through the BBB with optimized plasma pharmacokinetic properties. The results of the present investigation indicate that if the neurotrophic factor undergoes a defined molecular reformulation, such as that depicted in Fig. 1, both to enable BBB transport [biotin/OX26Mab] the addition of and to optimize plasma pharmacokinetics [Pegylation], then these molecules may have therapeutic effects in the brain after peripheral administration," see full article.

It would have been obvious at the time of the instantly claimed invention to PEGylate biphalin for the benefits of increased plasma half-life, reduced renal clearance, reduced cellular clearance, reduced proteolysis, reduced immunoclearance, reduced immunogenicity and antigenicity, and increased solubility among other as taught by Delgado et al. One would have been motivated to do so given that the benefits of PEGylation are not protein specific as also demonstrated by Delgado et al. One would have had a reasonable expectation of success given that many unrelated proteins have been PEGylated and shown to have these benefits and that PEGylation is a well-known and common modification in the peptide/protein arts. One would have been also further motivated with reasonable expectation of success to modify the PEG moiety to extend BBB transport as taught by Wu et al given Wu's clear teaching that this is extendable to many other neuropeptides with only the need for optimization. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the instantly claimed invention to PEGylate and conjugate the PEG to OX26/Strepavidin for improved pharmacokinetics and BBB transport.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Inada, et al, "Modification of Proteins with Polyethylene Glycol Derivatives," Methods in Enzymology, (1994), Vol 242, 65-90.

### **Conclusion**

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S. Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Application/Control Number: 10/647,561  
Art Unit: 1654

Page 6

Thomas S. Heard Ph.D.  
United States Patent and Trade Office  
Remsen 3B21  
(571) 272-2064  
Art Unit 1654



**Cecilia J. Tsang**  
**Supervisory Patent Examiner**  
**Technology Center 1600**